Exhibit A

FISH & RICHARDSON P.C.

225 Franklin Street
Boston, Massachusetts
02110-2804

Telephone
617 542-5070

Facsimile
617 542-8906

Web Site
www.fr.com

February 10, 2004

Karen A. Canella
U.S. Patent and Trademark Office (Patent)
Commissioner for Patents, Washington, DC 20231

Re: Predicting Survival Of Patients With Squamous Cell Carcinoma
Applicant: Mien-chie Hung et al.
Application No.: 09/637,190
Our Ref.: 12005-002001

Dear Examiner Canella:

Thank you for granting a telephone interview, scheduled for 2:00 pm, February 11, 2004 to resolve issues raised in the final office action. To facilitate discussion, we have outlined below our points, which are limited to claim 1.

1. Claim 1 was rejected as being obvious over Sager in view of Ding and 9 other references. This claim covers a method of determining a relative probability of survival for a subject with squamous cell carcinoma (SCC), based on a positive correlation between the maspin expression level in patients with SCC and the relative probability of survival for those patients. In the response filed October 3, 2003, we pointed out that Sager (1) teaches a method based on the discovery that the maspin level decreases during progression to breast cancer, and (2) does not teach that the maspin level decreases during progression to SCC. None of the secondary references mentions the down-regulation of the maspin level during SCC development. To the contrary, Ding states that the maspin level increases during progression to SCC and thereby teaches away from applying the Sager discovery to SCC.

Nonetheless, you countered that "Sager provides general teachings ... that the determination of whether or not a cell or tissue is cancerous or metastatic based on decreasing or absent levels of Maspin can be applied to any cell which normally expresses the Maspin gene[,including SCC]." (Emphasis added).

We disagree. It is well known in the art that a gene expressed in different types of cells may not be expressed in the same manner during development of cancers derived from them. As pointed out in our response filed on April 3, 2003, maspin is down-regulated in breast and prostate carcinomas but up-regulated in pancreatic and ovarian carcinomas. For example, Sood teaches that over-expression of maspin in ovarian carcinomas is indicative of high tumor grade and short survival. See Exhibit B attached to that response. Sood, citing Maass et al., also teaches that maspin is over-expressed in pancreatic cancers. According to Ding, "maspin was [also] commonly over-expressed in squamous cell carcinomas." In other words, one skilled in the art would recognize that Sager's "general" teachings are not reliable: it can be

applied to breast and prostate carcinomas but not to ovarian carcinomas, pancreatic cancers, and SCC. Accordingly, he or she would have neither the motivation nor a reasonable expectation of success to apply Sager's teachings on breast cancer to SCC. Thus, claim 1 is non-obvious over the cited references.

Here, we note that "[t]he test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts." (Emphasis added). See MPEP 2143.01. Thus, all above-discussed references must be considered. It is improper to consider only Sager and disregard Ding, Sood, and Maass.

2. You also rejected claim 1 for indefiniteness, asserting that the term "threshold level" recited in the claim is not defined. In our previous response, we pointed out that (1) this term is defined based on actual survival curves of a group of patients according to the assay described at page 2, paragraph 2 of the specification; and (2) the pre-determined levels of survival of the patients are used to determine corresponding threshold levels.

However, you maintained the rejection and countered that (1) "the [claim] do[es] not incorporate the survival curve;" (2) "the pre-determined levels of survival can be ... any value." We disagree.

First, according to case law, "[i]t is the function of the descriptive portion of the specification and not that of the claims to set forth operable proportions ... and that claims are not rendered indefinite by the absence of the recitation of such limitations." Ex parte Jackson, 217 USPQ 804 (POBA 1982). As a survival curve is just an operable proportion for the method of claim 1, claim 1 is not rendered indefinite by the absence of its recitation.

Second, contrary to the Examiner's assertion, the pre-determined levels of survival cannot be any values. Indeed, according to the specification, they are the levels "at which greater than 70% ... of patients survive for at least 50 months (page 2, paragraph 2)." In other words, the survival level at which 70% of patients survive for 50 months is the lower limit for the pre-determined levels of survival, and the corresponding maspin level is the lower limit for the threshold values.

To determine a relative probability of survival for a test subject with SCC, one measures the maspin levels of a group of patients and corresponding survival levels to obtain a survival curve. He or she then measures a test subject's maspin level and compares it to the survival curve thus obtained. If that subject's maspin level is above that at which 70% of patients survive for 50 months, the subject is prognozed to have a relatively high probability of survival. Thus, we submit that the term at issue is clearly defined and claim 1 is definite.

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We look forward to discussing with you the above issues at the interview. To expedite the prosecution, we would like to invite your supervisor Anthony Gaputa to this telephone interview. If you agree, please provide a copy of this letter to him before the interview.

Very truly yours,

Y. Rocky Tsao

Rocky Tsao, Ph.D., J.D.
Reg. No. 34,053

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